

12/29/98
JCS60 U.S. PRO

JCS41 U.S. PRO
60/114097
12/29/98

PATENT
IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT: J. Link, et al.

] Express Mail Label No. EE835516012US

SERIAL NO.: not yet assigned

] I hereby certify that this paper (along with any paper
] referred to as being attached or enclosed) is being
] deposited with the United States Postal Service as
] Express Mail Post Office to Addressee Service under 37
] C.F.R. 1.10 addressed to:

FILED: December 29, 1998

FOR: CELL ADHESION-INHIBITING
ANTIINFLAMMATORY AND
IMMUNE-SUPPRESSIVE COMPOUNDS

] Box Provisional Patent Application
] The Commissioner of Patents and Trademarks
] Washington, D.C.

EXAMINER: (not yet assigned)

] Date of Deposit: December 29, 1998

GROUP ART UNIT: (not yet assigned)

CASE NO. 6446.US.Z1

] *Kathleen T. Litz* 12/29/98
] Kathleen T. Litz DATE

DATE: December 29, 1998

TRANSMITTAL LETTER

Box Provisional Patent Application
The Commissioner of Patents and Trademarks
Washington D.C. 20231

Dear Sir:

Enclosed herewith is the Provisional patent application (Total pages: 100;
Specification: 91 pages; claims: 8 pages; abstract: 1 page) of J. Link, et al. for CELL
ADHESION-INHIBITING ANTIINFLAMMATORY AND IMMUNE-SUPPRESSIVE
COMPOUNDS.

Also enclosed are: Provisional Application Cover Sheet (in duplicate)
Return-Receipt Postcard

The Application Filing Fee, calculated as follows:

Basic Fee \$150.00

Total Filing Fee \$150.00

60114097-122998

Abbott Laboratories
Dept. 377 AP6D-2
100 Abbott Park Road
Abbott Park, IL 60064-4559
Tel. No. (847) 937-8272
Fax No. (847) 938-2623

Please type a plus sign (+) in this box → ☐

Approved for use through 1/31/98. OMB 0851-0037
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)					
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)			
James	Link	Evanston, IL			
Gang	Liu	Gurnee, IL			
Zhonghua	Pei	Libertyville, IL			
<input checked="" type="checkbox"/> Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
CELL ADHESION-INHIBITING ANTIINFLAMMATORY AND IMMUNE-SUPPRESSIVE COMPOUNDS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input type="checkbox"/> Customer Number		<input type="text"/>		Place Customer Number Bar Code Label here	
OR Type Customer Number here					
<input checked="" type="checkbox"/> Firm or Individual Name		Steven F. Weinstock, Abbott Laboratories			
Address		Dept. 377/AP6D			
Address		100 Abbott Park Road			
City		Abbott Park	State	IL	ZIP 60064-3500
Country			Telephone	847-937-8272	Fax (847) 983-2623
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages		<u>91</u>		<input type="checkbox"/> Small Entity Statement	
<input type="checkbox"/> Drawing(s) Number of Sheets		<input type="text"/>		<input type="checkbox"/> Other (specify) <u>Claims(8) Abstract(1)</u>	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees				FILING FEE AMOUNT (\$)	
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: <u>01-0025</u>				150	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____					

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Michael J. Ward

TELEPHONE (847) 937-8272

Date

12/29/98

REGISTRATION NO. 37,960

(if appropriate)

Docket Number: 6446.US.Z1

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

'15/1999 MHUNTER 00000025 010025 60114097
FC:114 150.00 CH

POSITION		ID NO.	DATE
CLASSIFIER		5	1/5-99
EXAMINER		68718	1/26/99
TYPIST		"	"
VERIFIER			
CORPS CORR.			
SPEC. HAND			
FILE MAINT			
DRAFTING			



PROVISIONAL PATENT APPLICATION IN ACCORDANCE WITH
35 U.S.C. 111(b) AND 37 C.F.R. 1.53 (b)(2)

CELL ADHESION-INHIBITING ANTIINFLAMMATORY
AND IMMUNE-SUPPRESSIVE COMPOUNDS

Technical Field

5 The present invention relates to compounds that are useful for treating inflammatory and immune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune response in a mammal.

Background of The Invention

10 Inflammation results from a cascade of events that includes vasodilation accompanied by increased vascular permeability and exudation of fluid and plasma proteins. This disruption of vascular integrity precedes or coincides with an infiltration of inflammatory cells. Inflammatory mediators generated at the site of the initial lesion serve to recruit inflammatory cells to the site of injury. These mediators (chemokines such as IL-8, MCP-1, MIP-1, and RANTES, complement fragments and lipid mediators)

15 have chemotactic activity for leukocytes and attract the inflammatory cells to the inflamed lesion. These chemotactic mediators which cause circulating leukocytes to localize at the site of inflammation require the cells to cross the vascular endothelium at a

precise location. This leukocyte recruitment is accomplished by a process called cell adhesion.

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then

5 cross the endothelial barrier to migrate to the inflamed tissue (Springer, T.A., 1994, Traffic Signals for Lymphocyte Recirculation and Leukocyte Emigration: The Multistep Paradigm, Cell 76: 301-314; Lawrence, M.B., and Springer, T.A., 1991, Leukocytes' Roll on a Selectin at Physiologic Flow Rates: Distinction from and Prerequisite for Adhesion Through Integrins, Cell.65: 859-873; von Adrian, U., Chambers, J.D., McEnvoy, L.M.,

10 Bargatze, R.F., Arfos, K.E, and Butcher, E.C., 1991, Two-Step Model of Leukocyte-Endothelial Cell Interactions in Inflammation, Proc. Natl. Acad. Sci. USA 88: 7538-7542; and Ley, K., Gaehtgens, P., Fennie, C., Singer, M.S., Lasky, L.H. and Rosen, S.D.,1991, Lectin-Like Cell Adhesion Molecule 1 Mediates Rolling in Mesenteric Venules *in vivo*, Blood 77: 2553-2555). These steps are mediated by families of adhesion

15 molecules such as integrins, Ig supergene family members, and selectins which are expressed on the surface of the circulating leukocytes and on the vascular endothelial cells. The first step consists of leukocytes rolling along the vascular endothelial cell lining in the region of inflammation. The rolling step is mediated by an interaction between a leukocyte surface oligosaccharide, such as Sialylated Lewis-X antigen (Slex),

20 and a selectin molecule expressed on the surface of the endothelial cell in the region of inflammation. The selectin molecule is not normally expressed on the surface of endothelial cells but rather is induced by the action of inflammatory mediators such as

TNF- α and interleukin-1. Rolling decreases the velocity of the circulating leukocyte in the region of inflammation and allows the cells to more firmly adhere to the endothelial cell. The firm adhesion is accomplished by the interaction of integrin molecules that are present on the surface of the rolling leukocytes and their counter-receptors (the Ig

5 superfamily molecules) on the surface of the endothelial cell. The Ig superfamily molecules or CAMs (Cell Adhesion Molecules) are either not expressed or are expressed at low levels on normal vascular endothelial cells. The CAM's, like the selectins, are induced by the action of inflammatory mediators like TNF-alpha and IL-1. The final event in the adhesion process is the extravasation of leukocytes through the endothelial

10 cell barrier and their migration along a chemotactic gradient to the site of inflammation. This transmigration is mediated by the conversion of the leukocyte integrin from a low avidity state to a high avidity state. The adhesion process relies on the induced expression of selectins and CAM's on the surface of vascular endothelial cells to mediate the rolling and firm adhesion of leukocytes to the vascular endothelium.

15 The interaction of the intercellular adhesion molecule ICAM-1 (cd54) on endothelial cells with the integrin LFA-1 on leukocytes plays an important role in endothelial-leukocyte contact. Leukocytes bearing high-affinity LFA-1 adhere to endothelial cells through interaction with ICAM-1, initiating the process of extravasation from the vasculature into the surrounding tissues. Thus, an agent which blocks the

20 ICAM-1/LFA-1 interaction suppresses these early steps in the inflammatory response. Consistent with this background, ICAM-1 knockout mice have numerous abnormalities in their inflammatory responses.

or a pharmaceutically-acceptable salt or prodrug thereof,

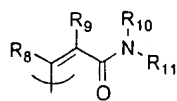
wherein R₁, R₂, R₃, R₄, and R₅ are independently selected from

5

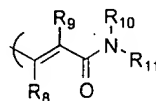
- a. hydrogen,
- b. halogen,
- c. alkyl,
- d. haloalkyl,
- 10 e. alkoxy,
- f. cyano,
- g. nitro,
- h. carboxaldehyde, and

15

with the proviso that at least one of R₁ or R₃ is a “*cis*-cinnamide” or a “*trans*-cinnamide”, defined as



“*cis*-cinnamide”



“*trans*-cinnamide”,

20

wherein R₈ and R₉ are independently selected from

- 5
- a. hydrogen, and
 - b. alkyl,
 - c. carboxy alkyl,
 - d. alkylaminocarbonyl alkyl, and
 - e. dialkylaminocarbonyl alkyl,

and R_{10} and R_{11} are independently selected from

- 10
- a. hydrogen,
 - b. alkyl,
 - c. cycloalkyl,
 - d. alkoxycarbonylalkyl,
 - e. hydroxyalkyl, and
- 15
- f. heterocyclalkyl,

or where $NR_{10}R_{11}$ is heterocycl or substituted heterocycl, where substituents are independently selected from

- 20
- 1) alkyl,
 - 2) alkoxy,
 - 3) alkoxyalkyl,
 - 4) cycloalkyl,

5

10

15

20

- 5) aryl,
- 6) heterocyclyl,
- 7) heterocyclylcarbonyl,
- 8) heterocyclylalkylaminocarbonyl,
- 9) hydroxy,
- 10) hydroxyalkyl,
- 11) hydroxyalkoxyalkyl,
- 12) carboxy,
- 13) carboxycarbonyl,
- 14) carboxaldehyde,
- 15) alkoxyalkyl,
- 16) arylalkoxyalkyl,
- 17) aminoalkanoyl,
- 18) carboxamido,
- 19) alkoxyalkylalkyl,
- 20) carboxamidoalkyl,
- 21) alkanoyl,
- 22) hydroxyalkanoyl,
- 23) alkanoyloxy,
- 24) alkanoylamino,
- 25) alkanoyloxyalkyl, and
- 26) alkylsulfonyl,

and wherein **Ar** is a substituted aryl or substituted heteroaryl group, where substitutions are independently selected from

- a. hydrogen,
- 5 b. halogen,
- c. alkyl,
- d. aryl,
- e. haloalkyl,
- f. hydroxy,
- 10 g. alkoxy,
- h. alkoxycarbonyl,
- i. alkoxyalkoxy,
- j. hydroxyalkyl,
- k. aminoalkyl,
- 15 l. alkyl(alkoxycarbonylalkyl)aminoalkyl,
- m. heterocyclalkyl,
- n. substituted heterocyclalkyl,
- o. carboxaldehyde,
- p. carboxaldehyde hydrazone,
- 20 q. carboxamide,
- r. alkoxycarbonyl alkyl,
- s. hydroxycarbonylalkyl (carboxyalkyl),

- t. cyano,
- u. amino,
- v. heterocyclalkylamino, and
- w. "trans-cinnamide".

5

In another embodiment of the invention are disclosed compounds represented by structural Formula I, above, when prepared by synthetic processes or by metabolic processes. Preparation of the compounds of the present invention by metabolic processes include those occurring in the human or animal body (*in vivo*) or by processes occurring

10 *in vitro*.

In another embodiment of the invention are disclosed methods of treatment or prophylaxis in which the inhibition of inflammation or suppression of immune response is desired, comprising administering an effective amount of a compound having Formula I.

15 In yet another embodiment of the invention are disclosed pharmaceutical compositions containing compounds of Formula I.

Detailed Description of The Invention

Definition of Terms

20 The term "alkanoyl" as used herein refers to an alkyl group attached to the parent molecular group through a carbonyl group.

The term "alkanoylamino" as used herein refers to an alkanoyl group attached to the parent molecular group through an amino group.

The term “alkanoyloxy” as used herein refers to an alkanoyl group attached to the parent molecular group through an oxygen radical.

The term “alkanoyloxyalkyl” as used herein refers to an alkanoyloxy group attached to the parent molecular group through an alkyl group.

5 The term “alkoxy” as used herein refers to an alkyl group attached to the parent molecular group through an oxygen atom.

The term “alkoxyalkoxy” as used herein refers to an alkoxy group attached to the parent molecular group through an alkoxy group.

10 The term “alkoxyalkyl” as used herein refers to an alkoxy group attached to the parent molecular group through an alkyl group.

The term “alkoxycarbonyl” as used herein refers to an alkoxy group attached to the parent molecular group through a carbonyl group.

The term “alkoxycarbonylalkyl” as used herein refers to an alkoxycarbonyl group attached to the parent molecular group through an alkyl group.

15 The term “alkyl” as used herein refers to a saturated straight or branched chain group of 1-10 carbon atoms derived from an alkane by the removal of one hydrogen atom.

The term “alkyl(alkoxycarbonylalkyl)amino” as used herein refers to an amino group substituted with one alkyl group and one alkoxycarbonylalkyl group.

20 The term “alkyl(alkoxycarbonylalkyl)aminoalkyl” as used herein refers to an alkyl(alkoxycarbonylalkyl)amino group attached to the parent molecular group through an alkyl group.

The term "alkylene" as used herein refers to a divalent group of 1-10 carbon atoms derived from a straight or branched chain alkane by the removal of two hydrogen atoms.

The term "alkylsulfonyl" as used herein refers to an alkyl radical attached to the parent molecular group through an $\text{-SO}_2\text{-}$ group.

The term "amino" as used herein refers to a radical of the form $\text{-NR}_{18}\text{R}_{19}$, or to a radical of the form $\text{-NR}_{18}\text{-}$, where R_{18} and R_{19} are independently selected from hydrogen, alkyl or cycloalkyl.

The term "aminoalkanoyl" as used herein refers to an amino group attached to the parent molecular group through an alkanoyl group.

The term "aminoalkyl" as used herein refers to an amino group attached to the parent molecular group through an alkyl group.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring. The aryl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy, or alkoxy substituents.

The term "arylalkoxy" as used herein refers to an aryl group attached to the parent molecular group through an alkoxy group.

The term "arylalkoxycarbonyl" as used herein refers to an arylalkoxy group attached to the parent molecular group through a carbonyl group.

The term "carboxaldehyde" as used herein refers to the radical -CHO .

The term "carboxaldehyde hydrazone" as used herein refers to the radical

-CH=N-NR₂₀R₂₁, where R₂₀ and R₂₁ are independently selected from hydrogen, alkyl or cycloalkyl.

The terms "carboxamide" or "carboxamido" as used herein refer to an amino group attached to the parent molecular group through a carbonyl group.

5 The term "carboxamidoalkyl" as used herein refers to a carboxamido group attached to the parent molecular group through an alkyl group.

The term "carboxy" as used herein refers to the radical -COOH.

The term "carboxycarbonyl" as used herein refers to a carboxy group attached to the parent molecular group through a carbonyl group.

10 The term "cyano" as used herein refers to the radical -CN.

The term "cycloalkyl" as used herein refers to a monovalent saturated cyclic or bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom. Cycloalkyl groups may be optionally substituted with alkyl, alkoxy, halo, or hydroxy substituents.

15 The terms "halo" or "halogen" as used herein refers to F, Cl, Br, or I.

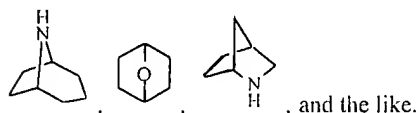
The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms.

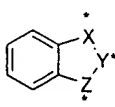
The terms "heterocycle" or "heterocyclyl" represent a 4-, 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" or "heterocyclic" as used herein additionally refers to bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to

20

one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

Heterocyclics also include bridged bicyclic groups where a monocyclic heterocyclic group is bridged by an alkylene group such as



Heterocyclics also include compounds of the formula  where X* and

Z* are independently selected from -CH₂-, -CH₂NH-, -CH₂O-, -NH- and -O-, with the proviso that at least one of X* and Z* is not -CH₂-, and Y* is selected from -C(O)- and -C(R'')₂-, where R'' is hydrogen or alkyl of one to four carbons, and v is 1-3. These

heterocycles include 1,3-benzodioxolyl, 1,4-benzodioxanyl, 1,3-benzimidazol-2-one and the like. The heterocycle groups of this invention can be optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents.

The term "heterocyclalkyl" as used herein refers to an heterocyclic group
5 attached to the parent molecular group through an alkyl group.

The term "heterocyclalkylamino" as used herein refers to an heterocyclalkyl group attached to the parent molecular group through an amino group.

The term "heterocyclalkylaminocarbonyl" as used herein refers to a
10 heterocyclalkylamino group attached to the parent molecular group through a carbonyl group.

The term "heterocyclcarbonyl" as used herein refers to a heterocycl group attached to the parent molecular group through a carbonyl group.

The term "hydroxyalkanoyl" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkanoyl group.

15 The term "hydroxyalkoxy" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkoxy group.

The term "hydroxyalkoxyalkyl" as used herein refers to an hydroxyalkoxy group attached to the parent molecular group through an alkyl group.

20 The term "hydroxyalkyl" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkyl group.

The term "perfluoroalkyl" as used herein refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluoride atoms.

The term "phenyl" as used herein refers to a monocyclic carbocyclic ring system having one aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. The phenyl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents.

5 The term "pharmaceutically-acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the
10 zwitterionic forms, where possible, of the compounds of the invention.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in
15 Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "thioalkoxy" as used herein refers to an alkyl group attached to the parent molecular group through a sulfur atom.

20 Compounds of the present invention can exist as stereoisomers wherein asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures

thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers are designated (\pm). Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Geometric isomers can also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the Z or E configuration wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. The arrangement of substituents around a carbocyclic ring are designated as cis or trans wherein the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated cis/trans.

- (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl)phenyl]
sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-acetyl) piperazin-1-yl)carbonyl)ethenyl)phenyl]
sulfide;
- 5 (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-pyridyl)piperazin-1-yl)carbonyl)
ethenyl)phenyl] sulfide;
- (2-(Hydroxymethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl]
sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;
- 10 (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)
ethenyl)phenyl] sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethoxyethyl)piperazin-1-yl)carbonyl)
ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl)
ethenyl)phenyl] sulfide;
- 15 (2-Bromophenyl)[2-chloro-4-(*E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl)
ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((3-(acetamidopyrrolidin-1-yl)carbonyl)ethenyl)phenyl]
sulfide;
- 20 (2-Bromophenyl)[2-chloro-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl]
sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((piperidin-1-yl)carbonyl) ethenyl)phenyl] sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]

- sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]
- sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((4-acetylhomopiperazin-1-yl)carbonyl)ethenyl)phenyl]
- 5 sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((4-(1-benzimidazol-2-onyl)piperidin-1-yl)carbonyl)
- ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-(*E*-((2-tetrahydroisoquinoliny)carbonyl)ethenyl)phenyl]
- 10 sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)
- ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl]
- sulfide;
- 15 (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((2-(1-morpholinyl)ethylamino)carbonyl)
- ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-phenylpiperazin-1-yl)carbonyl)
- ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((3-(1-pyrrolidin-2-
- 20 only)propylamino)carbonyl)ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((cyclopropylamino)carbonyl)ethenyl)phenyl]
- sulfide;
- (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]

sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,3-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]

5 sulfide;

(4-Bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(4-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

10 (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(methanesulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonylmethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

20 (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonylmethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

- (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxymethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- 5 (2-Chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-Aminophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-Hydroxymethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- 10 (2-Ethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-*iso*-Propylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-*tert*-Butylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- 15 (2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl))2-propenyl)phenyl] sulfide;
- (2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;
- 20 (2-(4-(1,3-Benzodioxolyl-5-methyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;
- (2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-

- morpholinyl)carbonyl) ethenyl)phenyl] sulfide;
- (2-((*N*-Ethoxycarbonylmethyl-*N*-methyl)aminomethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;
- (2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;
- 5 (2-(4-Formylpiperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;
- (2-(*E*-((1-Morpholinyl)carbonyl)ethenyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl) carbonyl)ethenyl)phenyl] sulfide;
- (2-Formylphenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]
- 10 sulfide;
- (2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide, *N,N*- dimethyl hydrazone;
- (2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;
- 15 (2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl) ethenyl)phenyl] sulfide;
- (2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;
- and
- (2-Chloro-6-formylphenyl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)
- 20 phenyl] sulfide.

Pharmaceutical Compositions and Methods of Treatment

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more pharmaceutically-acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of

microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically-acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner.

Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

5 Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl
10 benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as
15 wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and
20 tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository

wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The compounds of the present invention may be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. By "pharmaceutically-acceptable salt" is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are well-known in the art. For example, S. M. Berge, *et al.* Describe pharmaceutically-acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts may be prepared *in situ* during the final isolation and purification of the compounds of the

invention or separately by reacting a free base function with a suitable acid.

Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate,

- 5 fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such
- 10 agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to
- 15 form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

- Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing
- 20 moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically-acceptable basic addition salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium,

sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically-acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally dosage levels of about 0.1 to about 50 mg, more preferably of about 5 to about 20 mg of active compound per kilogram of body weight per day are administered orally or intravenously to a mammalian patient. If desired, the effective

daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

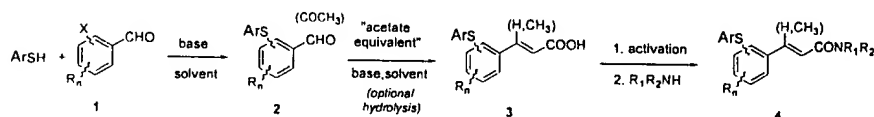
Preparation of Compounds of this Invention

5

The compounds and processes of the present invention may be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention can be prepared.

10

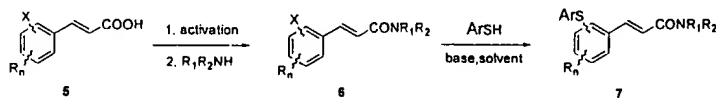
Scheme 1



Scheme 1 describes the synthesis of a typical cinnamide-substituted diaryl sulfide 4 through an aldehyde intermediate 2. Aldehyde 2 is prepared by reaction of a thiophenol (for example 2,4-dichlorothiophenol, 2-bromothiophenol, or the like) with halo-substituted benzaldehyde derivative 1 (e.g. 2-chlorobenzaldehyde, 3-chloro,4-fluorobenzaldehyde, or the like) in the presence of base (e.g. sodium carbonate, triethylamine, or the like) and a polar solvent (e.g. dimethylformamide, dimethylsulfoxide, or the like). The aldehyde group is homologated to the corresponding cinnamic acid 3, using an acetate equivalent (for example, malonic acid, triethoxyphosphonoacetate, or the like) in the presence of an appropriate base and

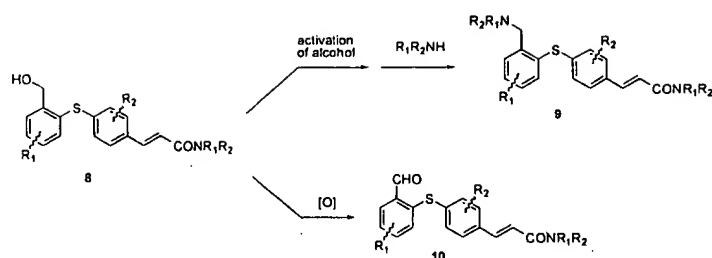
solvent. In some cases, it may be necessary to hydrolyze an intermediate ester (for example using sodium hydroxide in alcohol). The acid group is activated (for example using thionyl chloride, or dicyclohexylcarbodiimide and N-hydroxysuccinimide, or the like) and reacted with a primary or secondary amine (for example, 6-aminohexanol, pyrrolidone-3-propylamine, or the like) to provide the desired analog 4. In one variant, a halo-acetophenone can replace benzaldehyde 2; the resultant cinnamides 4 are substituted with a methyl group at the 3-position.

Scheme 2



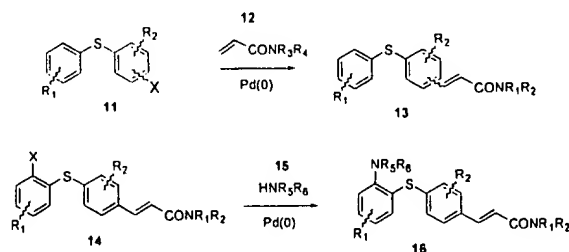
Alternatively, the order of these coupling steps may be reversed (Scheme 2). A substituted halocinnamic acid 5 (e.g. 3-chloro,2-nitrocinnamic acid or the like) may be coupled with a primary or secondary amine (e.g. N-acetylpiperazine or the like) as described above to give the corresponding amide 6. The halo-group can then be displaced with a substituted thiophenol in the presence of base to provide the product 7.

Scheme 3



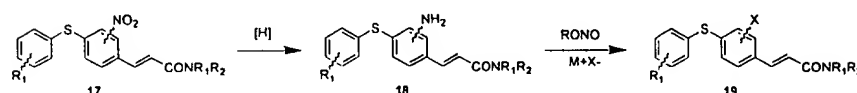
A number of the compounds described herein may be prepared from intermediate
 5 benzylic alcohols like 8 (Scheme 3) Activation of the alcohol moiety (for example, using
 phosphorus tribromide or methanesulfonyl chloride and lithium halide in
 dimethylformamide) and displacement with a primary or secondary amine (e.g.
 morpholine, N-formylpiperazine or the like) provides analogs with structures related to 9.
 Alternatively the alcohol may be oxidized (for example using TPAP or PCC or the like)
 10 to give aldehyde 10.

Scheme 4



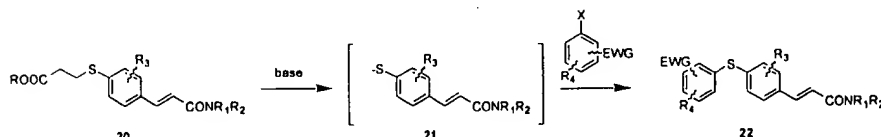
Cinnamides like **13** may be prepared from halo-substituted derivatives **11** by palladium-mediated coupling [e.g. using tetrakis (o-tolyl phosphine) palladium (0), $\text{Pd}_2(\text{dba})_3$, or the like] with acrylamide derivatives **12** (Scheme 4). In similar manner, anilino-cinnamides like **16** can be prepared by palladium-mediated coupling of amines **15** with halo-cinnamides **14**.

Scheme 5



In some cases, functional groups on the aromatic rings can be modified to produce new analogs (Scheme 5). For example, a nitro group in compounds like **17** may be reduced (for example, with tin(II) chloride, or by catalytic hydrogenation, or the like) to the corresponding amine **18**. This amine may then itself be converted to a halogen, for example by diazotization using nitrous acid or t-butyl nitrite in the presence of a metal halide salt like cupric bromide, providing analog **19**.

Scheme 6



It is also possible to assemble cinnamide-substituted diaryl sulfides in a "reverse" sense (Scheme 6). Thus, for example, compound 20, prepared as described in Scheme 1, may be deprotected by treatment with base (e.g. potassium t-butoxide or the like) to provide thiolate anion 21, which may be reacted with an activated haloarene (e.g. 2,3-dichlorobenzaldehyde, 3-chloro,4-fluorobenzaldehyde or the like) to provide the corresponding product 22.

The compounds and processes of the present invention will be better understood in connection with the following examples which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 1

(2,4-Dichlorophenyl)[2-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide

Example 1A

2-[(2,4-Dichlorophenyl)thio]benzaldehyde

To a stirred solution of 2,4-dichlorothiophenol (2.0 g, 11.2 mmol) in 25 mL of anhydrous DMF was added potassium carbonate (3.09 g, 22.4 mmol), followed by 2-chlorobenzaldehyde (1.26 mL, 11.3 mmol). The mixture was then heated under nitrogen atmosphere at 70 °C for 5 hours. The reaction mixture was then allowed to cool to room temperature and partitioned between ether and water. The aqueous layer was extracted with ether once and the combined organic layer was washed with water and brine, dried

over sodium sulfate and condensed in vacuo. The crude product was purified via silica gel flash chromatography, eluting with 5-10 % ether/hexanes, to give 2.62 g (9.25 mmol, 83%) of the desired aldehyde as a colorless oil, which solidified slowly upon standing at room temperature.

5

Example 1B

trans-2-[(2,4-Dichlorophenyl)thio]cinnamic acid

A mixture of the aldehyde (1.50 g, 5.3 mmol) from Example 1A, malonic acid (1.21 g, 11.6 mmol), piperidine (78.6 μ L, 0.80 mmol) in 8.0 mL of anhydrous pyridine was heated at 110 °C for 2 hours. Gas evolution ceased during this period. Pyridine was then removed under vacuum. Water and 3N aq. HCl were then added with stirring. The desired cinnamic acid was then collected through filtration, washed with cold water and dried in a vacuum oven overnight to give 1.56 g (4.8 mmol, 91 %) of white solid.

15

Example 1C

(2,4-Dichlorophenyl)[2-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide

A suspension of the acid (284 mg, 0.87 mmol) from Example 1B in 5 mL of methylene chloride was stirred with (COCl)₂ (84 μ L, 0.97 mmol), and one drop of DMF under nitrogen atmosphere for 90 minutes. The solvent was then removed under vacuum. The residue (COCl)₂ was removed with benzene (2x) in vacuo. To a separate flask, previously filled with 6-amino-1-hexanol (12 mg, 0.10 mmol), Hunig's base (22.8 μ L, 0.13 mmol) and DMAP (1.1 mg, 0.008 mmol) in 2.0 mL of CH₂Cl₂, the acid chloride (30

mg, 0.087 mmol) in 1.0 mL of CH₂Cl₂ was then dropped in slowly. After 30 minutes, the reaction mixture was poured into 3N HCl and extracted with ethyl acetate (EtOAc). The organic layer was washed with brine, dried with Na₂SO₄, condensed under reduced pressure. The crude product was purified by preparative TLC to give 21.0 mg (90 %) of the title compound as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 1.31-1.48 (m, 4H), 1.48-1.70 (m, 4H), 3.37 (q, *J* = 6.7 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 5.63 (br s, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.71 (d, *J* = 9.3 Hz, 1H), 7.05 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.31-7.49 (m, 4H), 7.65 (dd, *J* = 2.1, 7.5 Hz, 1H), 7.99 (d, *J* = 15.9 Hz, 1H). MS (DCI/NH₃) (M+NH₄)⁺ at *m/z* 441, 443, 445.

Example 2

(2,4-Dichlorophenyl)[2-(*E*-((3-(1-imidazolyl)propylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1C substituting 6-amino-1-hexanol with 1-(3-aminopropyl)imidazole. White powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.88 (p, *J* = 7.7 Hz, 2H), 3.11 (q, *J* = 7.7 Hz, 2H), 3.97 (t, *J* = 7.7 Hz, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 0.9 Hz, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 7.33 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.46-7.65 (m, 4H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.78 (d, *J* = 15.9 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 8.24 (t, *J* = 5.9 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 448, 450, 452. Analysis calculated for C₂₁H₁₉N₃O₁Cl₂S₁·0.87 H₂O: C, 56.30; H, 4.67; N, 9.38. Found: C, 56.30; H, 4.56; N, 9.27.

Example 3

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((2-hydroxyethylamino)carbonyl)
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

5 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with ethanolamine. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 3.57 (q, *J* = 7.65 Hz, 2H), 3.71 (q, *J* = 7.65 Hz, 2H), 6.06 (br s, 1H), 6.40 (d, *J* = 15.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 402, 404, 406, 408. Analysis calculated for C₁₇H₁₄N₁O₂Cl₃S₁·0.25H₂O: C, 50.14; H, 3.59; N, 3.44. Found: C, 50.16; H, 3.62; N, 3.29.

Example 4

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((6-hydroxyhexylamino)carbonyl)
ethenyl)phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.42 (m, 4H), 1.58 (m, 4H), 3.40 (q, *J* = 6.7 Hz, 2H), 3.65 (br m, 2H), 5.60 (br t, 1H), 6.35 (d, *J* = 15.3 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 458, 460, 462, 464. Analysis calculated for C₂₁H₂₂N₁O₂Cl₃S₁·0.27H₂O: C, 54.39; H, 4.90; N, 3.02. Found: C, 54.40; H, 4.85; N, 2.71.

Example 5

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((bis-(2-hydroxyethyl)amino)carbonyl)
ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

- 5 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with diethanolamine. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 2.99 (br s, 2H), 3.67 (br m, 4H), 3.88 (t, *J* = 5.1 Hz, 2H), 3.94 (t, *J* = 5.1 Hz, 2H), 6.94 (d, *J* = 15.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.21-7.32 (m, 3H), 7.50-7.54 (m, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 15.3 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 446, 448, 450, 452.
- 10 Analysis calculated for C₁₉H₁₈N₄O₃Cl₃S₁·1.09H₂O: C, 48.93; H, 4.36; N, 3.00. Found: C, 48.88; H, 4.00; N, 3.01.

Example 6

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)
ethenyl)phenyl] sulfide

15

The title compound was prepared by the procedures described in Example 1

- substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-(3-aminopropyl)-2-pyrrolidinone. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.74 (qu, *J* = 6.0 Hz, 2H), 2.09 (qu, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 8.25 Hz, 2H),
- 20 3.33 (q, *J* = 6.0 Hz, 2H), 3.42 (q, *J* = 8.25 Hz, 4H), 6.46 (d, *J* = 15.6 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 7.14-7.23 (m, 2H), 7.30 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 483,

485, 487, 489. Analysis calculated for $C_{22}H_{21}N_2O_2Cl_3S_1 \cdot 0.57H_2O$: C, 53.48; H, 4.52; N, 5.67. Found: C, 53.49; H, 4.60; N, 5.65.

Example 7

5 (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; 1H NMR ($CDCl_3$, 300 MHz) δ 3.59-3.80 (m, 8H), 6.83 (d, J = 15.6 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.16-7.32 (m, 3H), 7.49-7.53 (m, 1H),
10 7.59 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 15.6 Hz, 1H). MS (DCI/ NH_3) ($M+H$) $^+$ at m/z 428, 430, 432, 434. Analysis calculated for $C_{19}H_{16}N_1O_2Cl_3S_1 \cdot 0.46H_2O$: C, 52.22; H, 3.90; N, 3.20. Found: C, 52.20; H, 3.76; N, 3.12.

Example 8

15 (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-methylpiperazine. Colorless oil; 1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.51 (br m, 4H), 3.63-3.87 (br m, 4H), 6.85 (d, J = 15.6 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.19-7.25 (m, 2H), 7.27 (dd, J = 2.1, 8.7 Hz, 1H), 7.52 (t, J = 0.9 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H). MS (DCI/ NH_3) ($M+H$) $^+$ at m/z 441, 443, 445,

[illegible]

§

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-(4-acetyl)piperazin-1-yl)carbonyl
ethenyl)phenyl] sulfide

10

15

20

20

7.49-7.57 (m, 2H), 7.61 (d, $J = 15.6$ Hz, 1H), 7.62 (d, $J = 2.4$ Hz, 1H), 8.19-8.24 (m, 1H).

MS (DCI/NH₃) (M+H)⁺ at m/z 504, 506, 508, 510. Analysis calculated for

C₂₄H₂₀N₃O₁Cl₃S₁: C, 57.10; H, 3.99; N, 8.32. Found: C, 57.12; H, 4.06; N, 8.29.

5

Example 11

(2-(Hydroxymethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol, 2-

10 chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; ¹H NMR (CDCl₃, 300 MHz) δ 3.50-3.62 (br m, 6H), 3.65-3.74 (br m, 2H), 4.54 (d, $J = 5.7$ Hz, 2H), 5.33 (t, $J = 5.7$ Hz, 1H), 6.62 (d, $J = 8.7$ Hz, 1H), 7.28 (d, $J = 15.0$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 15.0$ Hz, 1H), 7.43 (dd, $J = 1.8, 8.7$ Hz, 1H), 7.50 (dd, $J = 2.1, 8.7$ Hz, 1H), 7.55 (dd, $J = 2.1, 7.8$ Hz, 1H), 7.68 (dd, $J = 1.5, 8.1$ Hz, 1H), 8.02 (d, $J = 2.1$ Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 390, 392.

15 Analysis calculated for C₂₀H₂₀N₁O₃Cl₁S₁ · 0.09H₂O: C, 61.35; H, 5.20; N, 3.58. Found: C, 61.37; H, 5.48; N, 3.81.

Example 12

20 (2-Bromophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with

3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.50-3.66 (br m, 6H), 3.66-3.79 (br m, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.26 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.33 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.36 (d, *J* = 15.6 Hz, 1H), 7.39 (dd, *J* = 1.8, 12.0 Hz, 1H), 7.45 (dd, *J* = 1.8, 6.3 Hz, 1H), 7.48 (d, *J* = 15.6 Hz, 1H), 7.64 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.80 (dd, *J* = 2.8, 8.7 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 438, 440, 442.

Example 13

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-hydroxyethylpiperazine. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 2.85-3.20 (br m, 6H), 3.84-4.19 (m, 6H), 6.80 (d, *J* = 15.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.22-7.38 (m, 3H), 7.50-7.56 (m, 1H), 7.56-7.62 (m, 1H), 7.60 (d, *J* = 15.3 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 471, 473, 475, 477.

Example 14

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-hydroxyethoxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-

hexanol with 1-[2-(2-hydroxyethoxy)ethyl]piperazine. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 2.73 (br m, 6H), 3.58-3.68 (m, 2H), 3.68-4.00 (m, 8H), 6.84 (d, *J* = 15.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.20-7.34 (m, 3H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 15.3 Hz, 1H), 7.58-7.65 (overlapping d, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 515, 517, 519, 521.

Example 15

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-hydroxymethylpiperidine. ¹H NMR (DMSO-*d*₆, 300MHz) δ 8.07 (d, *J* = 17.7 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.63 (br d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.0 Hz, 1H), 7.40 (br s, 2H), 7.35 (m, 1H), 7.25 (dd 7.7, 1.5, 1H), 7.06 (dd, *J* = 8.1, 2.9, 1H), 4.57 (m, 1H), 4.45 (m, 1H), 4.16 (br m, 2H), 1.2 – 1.8 (m, 8H). HRMS calculated for C₂₁H₂₁N₁O₂S₁Br₁Cl₁: 466.0243. Observed: 466.0247.

Example 16

(2-Bromophenyl)[2-chloro-4-(*E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 2-hydroxymethylpiperidine. ¹H NMR (DMSO-d₆, 300MHz) δ 8.03 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.61 (m, 1H), 7.30 – 7.45 (m, 4H), 7.23 (m, 1H), 7.07 (m, 1H), 4.79 (m, 2H), 4.61 (m, 2H), 4.10 (m, 1H), 1.50 (m, 6H). HRMS calculated for C₂₁H₂₁N₁O₂S₁Br₁Cl₁: 466.0243. Observed: 466.0247.

Example 17

(2-Bromophenyl)[2-chloro-4-(*E*-((3-acetamidopyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-acetamidopyrrolidine. ¹H NMR (DMSO-d₆, 300MHz) δ 8.14 (m, 1H), 8.07 (dd, *J* = 9.8, 1.7 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.25 – 7.47 (m, 4H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.45 – 4.34 (m, 6H), 2.02 (m, 2H), 1.81 (ap d, *J* = 1.4 Hz, 1H). HRMS calculated for C₂₁H₂₀N₂O₂S₁Br₁Cl₁: 479.0196. Observed: 479.0183.

Example 18

(2-Bromophenyl)[2-chloro-4-(*E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-hydroxypiperidine. ¹H NMR (DMSO-d₆, 300MHz) δ 8.08 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.44 (ap dd, *J* = 7.5, 1.4 Hz, 2H), 7.40 (ap d, *J* = 3.7 Hz, 2H), 7.34 (dt, *J* = 7.6, 1.8 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 4.76 (br s, 1H), 4.01 (m, 2H), 3.72 (m, 1H), 3.12 (m, 1H), 1.75 (m, 2H), 1.32 (m, 2H). HRMS calculated for C₂₀H₁₉N₁O₂S₁Br₁Cl₁: 452.0087. Observed: 452.0076.

Example 19

(2-Bromophenyl)[2-chloro-4-(*E*-((piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with piperidine. ¹H NMR (DMSO-d₆, 300MHz) δ 8.08 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.44 (ap dd, *J* = 7.6, 1.5 Hz, 1H), 7.39 (ap d, *J* = 4.8 Hz, 2H), 7.34 (dt, *J* = 7.5, 1.6, 1H), 7.24 (dd, *J* = 7.5, 1.7, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 3.65 (br m, 2H), 3.53 (br m, 2H), 1.62 (br m, 2H), 1.50 (br m, 4H). HRMS calculated for C₂₀H₁₉N₁O₁S₁Br₁Cl₁: 436.0130. Observed: 436.0122.

Example 20

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with nipecotic acid. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.44-1.68 (br m, 1H), 1.68-2.00 (br m, 2H), 2.51-2.67 (br m, 1H), 3.13-3.37 (br m, 1H), 3.80-4.12 (br m, 1H), 4.30-5.00 (br m, 3H), 6.86 (d, *J* = 15.3 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.16-7.24 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.47-7.55 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.60 (br d, 1H). MS (APCI) (M+H)⁺ at *m/z* 470, 472, 474, 476.

10

Example 21

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with isonipecotic acid. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.68-1.85 (m, 2H), 1.98-2.09 (m, 2H), 2.60-2.72 (m, 1H), 2.90-3.13 (br m, 1H), 3.17-3.38 (br m, 1H), 3.93-4.12 (br m, 1H), 4.38-4.59 (br m, 1H), 6.86 (d, *J* = 15.3 Hz, 1H), 6.99 (dd, *J* = 8.7 Hz, 1H), 7.20-7.25 (m, 2H), 7.28 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.49-7.53 (m, 1H), 7.56 (d, *J* = 15.3 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 470, 472, 474, 476.

20

Example 22

(2-Bromophenyl)[2-chloro-4-(*E*-((4-acetylhomopiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

- 5 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-acetylhomopiperazine.

¹H NMR (DMSO-d₆, 300MHz) δ 8.10 (m, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.64 (m, 1H), 7.24 – 7.51 (m, 5H), 7.05 (m, 1H), 3.39 – 3.77 (m, 8H), 1.97 (m, 3H), 1.68 (m, 2H).

HRMS calculated for C₂₂H₂₂N₂O₂S₁Br₁Cl₁: 493.0352. Observed: 493.0352.

10

Example 23

(2-Bromophenyl)[2-chloro-4-(*E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

- substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with thiomorpholine. ¹H NMR

(DMSO-d₆, 300MHz) δ 8.10 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.31 – 7.48 (m, 4H), 7.36 (m, 1H), 7.26 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 3.96 (m, 2H), 3.82 (m, 2H), 2.62 (m, 4H). HRMS calculated for

C₁₉H₁₇N₁O₁S₂Br₁Cl₁: 455.9681. Observed: 455.9676.

20

Example 24

(2-Bromophenyl)[2-chloro-4-(*E*-((1-benzimidazol-2-onyl)piperidin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-(1-benzimidazol-2-
5 only)piperidine. ¹H NMR (DMSO-d₆, 300MHz) δ 8.14 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.48 (ap s, 2H), 7.44 (dt, *J* = 7.5, 1.2, 1H), 7.34 (dt, *J* = 7.6, 1.6, 1H), 7.26 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.22 (m, 1H), 7.06 (d, *J* = 8.1, 1H), 6.97 (ap d, *J* = 2.6, 3H), 4.64 (m, 1H), 4.48 (m, 2H), 2.79 (m, 2H), 2.29 (m, 2H), 1.78 (m, 2H). HRMS calculated for C₂₇H₂₃N₃O₂S₁Br₁Cl₁: 568.0461. Observed:
10 568.0477.

Example 25

(2-Bromophenyl)[2-chloro-4-(*E*-((2-tetrahydroisoquinolinyl)carbonyl)

ethenyl)phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with tetrahydroisoquinoline. ¹H
NMR (DMSO-d₆, 300MHz) δ 8.12 (d, *J* = 7.4 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.1 Hz, 1H),
7.67 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.47 (m, 2H), 7.43 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.34 (dt, *J* =
20 7.6, 1.7 Hz, 1H), 7.27 (d 7.7 Hz, 1H), 7.19 (m, 4H), 7.05 (d, *J* = 8.1 Hz, 1H), 4.92 (s, 1H),
4.72 (s, 1H), 3.95 (t, *J* = 5.9 Hz, 1H), 3.78 (t, *J* = 5.7 Hz, 1H), 2.89 (t, *J* = 5.3 Hz, 1H), 2.83

[illegible]

5

10

15

20

49

1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.87 (d, J = 14.0 Hz, 1H); 6.84 (d, J = 7.6 Hz, 1H); 3.73 (br s, 8H); 2.34 (s, 3H). MS (ESI) *m/z* 837 (2M+Na)⁺, 815 (2M+H)⁺, 408 (M+H)⁺.

Example 28

5 (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((2-(1-morpholinyl)ethylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 2-(1-morpholinyl)ethylamine. ¹H NMR (CDCl₃, 300MHz) δ 7.80 (s, 1H); 7.56 (d, J = 15.8 Hz, 1H); 7.50 (d, J = 8.1 Hz, 1H); 7.40-7.32 (m, 3H); 7.28 (m, 1H); 6.79 (d, J = 15.8 Hz, 1H); 6.40 (d, J = 8.1 Hz, 1H); 3.75 (t, J = 4.6 Hz, 4H); 3.51 (q, J = 5.5 Hz, 2H), 2.57 (t, J = 5.8 Hz, 2H); 2.55-2.48 (m, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 923 (2M+Na)⁺, 473 (M+Na)⁺, 451 (M+H)⁺.

15

Example 29

20 (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-phenylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 4-phenylpiperazine. ¹H NMR (CDCl₃, 300MHz) δ 7.81 (s, 1H); 7.64 (d, J = 16.0 Hz, 1H); 7.51 (d, J = 8.2 Hz,

1H); 7.40-7.27 (m, 6H); 6.98-6.90 (m, 4H); 6.80 (d, J = 8.2 Hz, 1H); 3.88 (br s, 4H); 2.23 (br s, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 987 (2M+Na)⁺, 965 (2M+H)⁺, 505 (M+Na)⁺, 483 (M+H)⁺, 451.

5

Example 30

(2-Methylphenyl)[2-trifluoromethyl-4-(E-((3-(1-pyrrolidin-2-
only)propylamino)carbonyl)
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1
10 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with
4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 1-pyrrolidin-2-
only)propylamine. ¹H NMR (CDCl₃, 300MHz) δ 7.78 (s, 1H); 7.53 (d, J = 15.6 Hz, 1H);
7.49 (d, J = 7.2 Hz, 1H); 7.40-7.33 (m, 3H); 7.14 (m, 1H); 6.80 (d, J = 8.2 Hz, 1H); 6.43
(d, J = 15.6 Hz, 1H); 3.41 (m, 4H); 3.32 (q, J = 6.1 Hz, 2H); 2.43 (t, J = 6.6 Hz, 2H); 2.34
15 (s, 3H), 2.08 (m, 2H), 1.75 (m, 2H). MS (ESI) *m/z* 947 (2M+Na)⁺, 925 (2M+H)⁺, 485
(M+Na)⁺, 463 (M+H)⁺.

Example 31

(2-Methylphenyl)[2-trifluoromethyl-4-(E-((cyclopropylamino)carbonyl)
ethenyl)phenyl] sulfide

20

The title compound was prepared by the procedures described in Example 1 substituting
2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-

trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with cyclopropylamine. ¹H NMR (CDCl₃, 300MHz) δ 7.76 (s, 1H); 7.56 (d, J = 15.4 Hz, 1H); 7.50 (d, J = 8.4 Hz, 1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.88 (d, J = 8.4 Hz, 1H); 6.30 (d, J = 15.4 Hz, 1H); 5.70 (br s, 1H), 2.95 (m, 1H); 2.34 (s, 3H); 0.85 (m, 2H); 0.57 (m, 2H). MS (ESI) *m/z* 777 (2M+Na)⁺, 755 (2M+H)⁺, 400 (M+Na)⁺, 378 (M+H)⁺.

Example 32

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Example 32A

1-Chloro-2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) benzene

To a stirred solution of *trans*-4-chloro-3-nitrocinnamic acid (1.50 g, 6.59 mmol) and 1-acetylpiperazine (0.89 g, 6.94 mmol) in 20 mL of DMF at room temperature was added EDAC (1.4 g, 7.30 mmol). The mixture was then stirred at room temperature for 2 hours. TLC indicated the complete consumption of the acid. Water was then added to quench the reaction and to precipitate out the product. Cinnamide was then collected through filtration and washed with cold water. The light yellow product was dried in vacuum oven overnight at 40 °C to give 2.04 g (6.03 mmol, 91.6 %) of the title compound.

Example 32B

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

To a stirred solution of 4-chloro-3-nitro-cinnamide (275 mg, 0.814 mmol) from Example 32A in 1.0 mL of DMF was added potassium carbonate (169 mg, 1.22 mmol), followed by the dropwise addition of 2,4-dichlorothiophenol (146 mg, 0.815 mmol).

- 5 The mixture was then stirred at room temperature for 60 minutes. Completion of the reaction was indicated by the TLC. Water was then added to precipitate the product. Filtration, washing with cold water, and drying in a vacuum oven afforded 350 mg (0.728 mmol, 89%) of the titled compound as light yellow solid. ¹H NMR (d⁶-DMSO, 300 MHz): δ 2.05 (s, 3H), 3.42-3.50 (br m, 4H), 3.50-3.64 (br m, 2H), 3.64-3.79 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 15.3 Hz, 1H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 497, 499, 501. Analysis calculated for C₂₁H₁₉N₃O₄ Cl₂ S·0.82H₂O: C, 50.94; H, 4.20; N, 8.49. Found: C, 50.91; H, 4.21; N, 8.69.
- 10

15

Example 33

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)

ethenyl)phenyl] sulfide

- The title compound was prepared by the procedures described in Example 32 substituting 1-acetypiperazine with 1-(3-aminopropyl)-2-pyrrolidinone. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.64 (p, *J* = 7.1 Hz, 2H), 1.91 (p, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 8.3 Hz, 2H), 3.15 (q, *J* = 6.3 Hz, 2H), 3.21 (dd, *J* = 9.9, 17.7 Hz, 2H),
- 20

3.32 (overlapping t, $J = 8.4$ Hz, 2H), 6.72 (d, $J = 15.6$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 1H), 7.46 (d, $J = 15.6$ Hz, 1H), 7.63 (dd, $J = 2.4, 8.1$ Hz, 1H), 7.79 (dd, $J = 2.4, 8.7$ Hz, 1H), 7.84 (d, $J = 8.7$ Hz, 1H), 7.96 (d, $J = 2.4$ Hz, 1H), 8.18 (t, $J = 6.0$ Hz, 1H), 8.46 (d, $J = 2.1$ Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 494, 496.

5

Example 34

(2,3-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

The title compound was prepared by the procedures described in Example 32B

10 substituting 2,4-dichlorothiophenol with 2,3-dichlorothiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.42-3.50 (br m, 4H), 3.50-3.64 (br m, 2H), 3.64-3.79 (br m, 2H), 6.88 (d, $J = 8.7$ Hz, 1H), 7.45 (d, $J = 15.6$ Hz, 1H), 7.55 (t, $J = 7.65$ Hz, 1H), 7.57 (d, $J = 15.6$ Hz, 1H), 7.78 (dd, $J = 1.8, 8.1$ Hz, 1H), 7.87 (dd, $J = 1.8, 8.1$ Hz, 1H), 7.95 (dd, $J = 2.7, 9.0$ Hz, 1H), 8.69 (d, $J = 1.8$ Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 497, 499, 501.

Example 35

(4-Bromophenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 32

20 substituting 2,4-dichlorothiophenol with 4-bromothiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 7.43 (d, $J = 15.0$ Hz, 1H),

7.54 (d, $J = 15.0$ Hz, 1H), 7.58 (d, $J = 9.0$ Hz, 2H), 7.78 (d, $J = 9.0$ Hz, 2H), 7.92 (dd, $J = 2.1, 9.0$ Hz, 1H), 8.65 (d, $J = 2.1$ Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 507, 509.

Example 36

5 (4-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with *p*-thiocresol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 2.39 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 6.89 (d, $J = 8.7$ Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 1H), 7.39 (d, $J =$
10 8.4 Hz, 2H), 7.40 (d, $J = 15.0$ Hz, 1H), 7.53 (d, $J = 15.0$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.89 (dd, $J = 2.1, 8.7$ Hz, 1H), 8.64 (d, $J = 2.1$ Hz, 1H). MS (DCI/NH₃) (M+NH₄)⁺ at m/z 443.

Example 37

15 (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 1-acetylpiperazine with *tert*-butyl piperazine carboxylate. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.42 (s, 9H), 3.36 (overlapping m, 4H), 3.55
20 (br m, 2H), 3.70 (br m, 2H), 6.83 (d, $J = 8.7$ Hz, 1H), 7.42 (d, $J = 15.6$ Hz, 1H), 7.54 (d, $J = 15.6$ Hz, 1H), 7.63 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 1H), 7.92 (dd, $J = 2.4,$

8.7 Hz, 1H), 7.96 (d, J = 2.7 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H). MS (APCI) (M+H)⁺ at m/z 538, 540, 542.

Example 38

5 (2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Example 38A

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Trifluoroacetic Acid Salt

10 The compound (100 mg, 0.186 mmol) from Example 37 was dissolved in 0.5 mL of neat trifluoroacetic acid (TFA). The mixture was stirred at room temperature for 1 hour. The TFA was then removed under vacuum to give the title compound (105 mg) as a yellow solid.

Example 38B

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

15 To a stirred solution of piperazine TFA salt (35 mg, 0.067 mmol) from Example 38A in 2.0 mL of CH₂Cl₂ was added Et₃N (23 μ L, 0.17 mmol), 4-dimethylaminopyridine (DMAP) (1.0 mg, 0.0082 mmol), and furyl chloride (8.0 μ L, 0.080 mmol). The mixture was then stirred at room temperature for 30 minutes before the solvent was removed. The

crude product was purified with Gilson HPLC system, YMC C-18 column, 75x30 mm I.D., S-5 μ M, 120 Å, and a flow rate of 25 mL/min, λ =214, 245 nm; mobile phase A, 0.05 M NH_4OAc , and B, CH_3CN ; linear gradient 20-100% of B in 20 minutes to give the title compound (24 mg, 67%) as light-yellow powder; ^1H NMR (d^6 -DMSO, 300 MHz) δ 3.62-3.87 (br m, 8H), 6.66 (q, J = 2.1 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 3.3 Hz, 1H), 7.44 (d, J = 15.3 Hz, 1H), 7.56 (d, J = 15.3 Hz, 1H), 7.63 (dd, J = 2.4, 8.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 2.1, 12.0 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H). MS (APCI) ($\text{M}+\text{H}$) $^+$ at m/z 532, 534, 536.

Example 39

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(methanesulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with methanesulfonyl chloride. Light-yellow powder; ^1H NMR (d^6 -DMSO, 300 MHz) δ 2.90 (s, 3H), 3.25 (br m, 4H), 3.68 (br m, 2H), 3.83 (br m, 2H), 6.84 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 15.6 Hz, 1H), 7.63 (dd, J = 2.4, 8.7 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.93 (dd, J = 2.1, 9.0 Hz, 1H), 7.95 (d, J = 2.7 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H). MS (ESI) ($\text{M}+\text{H}$) $^+$ at m/z 516, 518, 520.

Example 40

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonylmethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with 2-chloro-*N,N*-diethylacetamide. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 2.46 (br m, 4H), 3.16 (s, 2H), 3.24 (q, *J* = 7.2 Hz, 2H), 3.37 (q, *J* = 7.2 Hz, 2H), 3.56 (br m, 2H), 3.69 (br m, 2H), 6.83 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 15.3 Hz, 1H), 7.52 (d, *J* = 15.3 Hz, 1H), 7.62 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.92 (dd, *J* = 2.1, 9.0 Hz, 1H), 7.95 (d, *J* = 2.7 Hz, 1H), 8.67 (d, *J* = 2.1 Hz, 1H). MS (ESI) (M+NH₄)⁺ at *m/z* 573, 575, 577.

Example 41

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with *N,N*-diethylcarbonyl chloride. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.06 (t, *J* = 6.9 Hz, 6H), 3.12 (br m, 4H), 3.15 (q, *J* = 6.9 Hz, 4H), 3.58 (br m, 2H), 3.72 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.95 (d, *J* = 2.7 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 537, 539, 541.

Example 42

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(*tert*-butoxycarbonylmethyl)piperazin-1-yl))

carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting CH₂CL₂ with CH₃CN as solvent, and furoyl chloride with *tert*-butyl bromoacetate. Light-yellow powder; ¹H NMR (CDCl₃, 300 MHz) δ 1.47 (s, 9H), 2.70 (br m, 4H), 3.21 (s, 2H), 3.74 (br m, 2H), 3.82 (br m, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 15.0 Hz, 1H), 7.39 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 15.0 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 8.43 (br d, 1H). MS (APCI) (M+H)⁺ at *m/z* 552, 554, 556.

Example 43

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

Example 43A

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carbethoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with ethyl oxalyl chloride.

Example 43B

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

To a stirred solution of the ethyl ester (40 mg, 0.074 mmol) from Example 43A in 2 mL of ethanol was added saturated LiOH (0.25 mL). The mixture was then stirred at room temperature for 2 hours. Water (2 mL) was then added to the reaction mixture, which was then acidified to pH = 2 with concentrated HCl. The precipitates were collected through filtration, washed with cold water, dried under vacuum to give the titled compound (30 mg, 79%) as light yellow solid. ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.52 (br m, 4H), 3.62 (br m, 2H), 3.76 (br m, 2H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 15.3 Hz, 1H), 7.56 (d, *J* = 15.3 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.70 (br d, 1H). MS (APCI) (M-COO)⁺ at *m/z* 466, 468, 470.

Example 44

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxymethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38A substituting compound from Example 37 with compound from Example 42. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.14 (s, 2H), 3.40 (overlapping br m, 4H), 3.44 (br m, 1H), 3.51 (br m, 1H), 3.57 (br m, 1H), 3.71 (br m, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.52 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 496, 498, 500.

Example 45

(2-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

5 The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with *o*-thiocresol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.03 (s, 3H), 2.29 (s, 3H), 3.47 (br m, 4H), 3.53 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.83 (br m, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 15.0 Hz, 1H), 7.36-7.42 (m, 1H), 7.46-7.57 (m, 3H), 7.63 (d, *J* = 6.9 Hz, 1H), 7.89 (dd, *J* = 2.4, 9.0
10 Hz, 1H), 8.66 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 426.

Example 46

(2-Chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32
15 substituting 2,4-dichlorothiophenol with 2-chlorothiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.73 (br m, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 15.3 Hz, 1H), 7.54 (d, *J* = 15.3 Hz, 1H), 7.55 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.64 (t, *J* = 1.8, 8.1 Hz, 1H), 7.76 (d, *J* = 1.8, 8.1 Hz, 1H), 7.82 (d, *J* = 1.8, 8.1 Hz, 1H), 7.93 (dd, *J* = 2.4, 9.0 Hz, 1H),
20 8.68 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 446, 448, 450.

Example 47

(2-Aminophenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-aminothiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 5.58 (s, 2H), 6.65 (td, *J* = 1.5, 15.0 Hz, 1H), 6.72 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.00 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.27 (t, *J* = 1.5, 8.6 Hz, 1H), 7.36 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.39 (d, *J* = 15.3 Hz, 1H), 7.53 (d, *J* = 15.3 Hz, 1H), 7.89 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 427.

Example 48

(2-Hydroxymethylphenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.03 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 4.53 (d, *J* = 5.7 Hz, 1H), 5.34 (t, *J* = 5.7 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 15.3 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 15.3 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.87 (dd, *J* = 2.1, 8.7 Hz, 1H), 8.65 (d, *J* = 2.1 Hz, 1H). MS (APCI) (M+NH₄)⁺ at *m/z* 459.

Example 49

(2-Ethylphenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-ethylthiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.01 (t, *J* = 7.65 Hz, 3H), 2.04 (s, 3H), 2.69 (q, *J* = 7.65 Hz, 2H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.59 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 2.4, 7.5 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.50-7.61 (m, 3H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.89 (dd, *J* = 2.4, 8.7 Hz, 1H), 8.64 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+Cl)⁻ at *m/z* 474, 476.

Example 50

(2-*iso*-Propylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-isopropylthiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.05 (d, *J* = 6.9 Hz, 6H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.72 (br m, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.34-7.41 (m, 2H), 7.39 (d, *J* = 15.3 Hz, 1H), 7.52 (d, *J* = 15.3 Hz, 1H), 7.56-7.73 (m, 2H), 7.90 (dd, *J* = 2.1, 8.7 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H). MS (APCI) (M+NH₄)⁺ at *m/z* 471. Analysis calculated for C₂₄H₂₇N₃O₄ S₁·0.21H₂O: C, 63.03; H, 5.96; N, 9.13. Found: C, 63.03; H, 6.04; N, 9.19.

Example 51

(2-*tert*-Butylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-*tert*-butylthiophenol. Light-yellow powder; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.46 (s, 9H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 15.3 Hz, 1H), 7.45-7.57 (m, 2H), 7.50 (d, *J* = 15.3 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.88 (dd, *J* = 2.4, 8.7 Hz, 1H), 8.64 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+NH₄)⁺ at *m/z* 485.

Example 52

(2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)) 2-propenyl)phenyl] sulfide

Example 52A

3'-Chloro-4'-[(2-chlorophenyl)thio]acetophenone

The title compound was prepared by the procedures described in Example 1A substituting 2,4-dichlorothiophenol with 2-chlorothiophenol, and 2-chlorobenzaldehyde with 4'-fluoro-3'-chloroacetophenone.

Example 52B

(2-Chlorophenyl)[2-chloro-4-(*E*-(1-ethoxycarbonyl) 2-propenyl)phenyl] sulfide

To a stirred suspension of NaH (60% in mineral oil, 121 mg, 3.03 mmol) in 20 mL of anhydrous THF under nitrogen atmosphere was added triethyl phosphonoacetate

dropwise. After 20 minutes, the acetophenone (600 mg, 2.02 mmol) from Example 52A in THF (5 mL) was added in one portion. The resulting clear solution was then stirred at room temperature for 7 hours. Reaction was then stopped, most of the solvent was evaporated, and the residue was partitioned between EtOAc (2x20 mL) and water. The combined organic layer was washed with water and brine, dried over Na₂SO₄, concentrated in vacuo. The crude product was purified using silica gel flash column chromatography eluting with 5-10% Et₂O in hexanes to give the (*E*)-isomer of the cinnamate (500 mg, 68%) as a white solid.

Example 52C

(2-Chlorophenyl)[2-chloro-4-(*E*-(1-carboxy) 2-propenyl)phenyl] sulfide

A mixture of the cinnamate (500 mg, 1.37 mmol) from Example 52B in 5 mL of EtOH/THF (4:1) was stirred with sat. LiOH solution (0.50 mL) at 50 °C for 2 hours. The mixture was then acidified with 3N HCl and extracted with CH₂Cl₂ (3x10 mL). The combined organic layer was dried over MgSO₄, concentrated under reduced pressure to give the titled compound (450mg, 97%) as a white solid.

Example 52D

(2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)

2-propenyl)phenyl] sulfide

The title compound was prepared using the cinnamic acid from Example 52C by the procedures described in Example 1C substituting 6-amino-1-hexanol with 1-

acetylpiperazine. White solid; ¹H NMR (CDCl₃, 300 MHz) δ 2.10-2.20 (m, 3H), 2.25 (s, 3H), 3.40-3.80 (m, 8H), 6.28 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 7.19-7.36 (m, 4H), 7.46-7.56 (m, 2H). MS (APCI) (M+NH₄)⁺ at *m/z* 466, 468, 470.

5

Example 53

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl) phenyl] sulfide

10
15
20

Example 53A

(2-(1-Bromomethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl) phenyl] sulfide

To a stirred solution of benzyl alcohol (195 mg, 0.32 mmol) from Example 11 in 2.0 mL of anhydrous DMF was added LiBr (48 mg, 0.35 mmol). The mixture was then cooled in an ice-water bath, and PBr₃ (60 μL, 0.40 mmol) was dropped in slowly. The ice bath was then removed and the mixture was stirred at room temperature for 1 hour. Water was then added, the mixture was then partitioned between EtOAc and aqueous NaHCO₃. The aqueous layer was extracted with EtOAc once. The combined organic layer was washed with water and brine, dried over Na₂SO₄, concentrated on a rotavap. The crude bromide (230mg) was used directly for the alkylation without purification.

20

Example 53B

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)

ethenyl) phenyl] sulfide

To a stirred solution of morpholine (10 μ L, 0.11 mmol) in 0.5 mL of CH_3CN was added Hunig base (23.7 μ L, 0.14 mmol), followed by the bromide (40 mg, 0.091 mmol).

The mixture was then stirred at room temperature for 2 hours. Solvent was then removed

5 and the crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a white solid. ^1H NMR (d^6 -DMSO, 300 MHz) δ 2.33 (br t, 4H), 3.45 (br t, 4H), 3.50-3.65 (m, 6H), 3.56 (s, 2H), 3.65-3.80 (br m, 2H), 6.74 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 15.3 Hz, 1H), 7.35-7.41 (m, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.46 (td, J = 2.4, 8.1 Hz, 1H), 7.52 (dd, J = 2.1, 8.7 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H). MS (DCI/ NH_3) ($\text{M}+\text{H}$) $^+$ at m/z 459, 461.

Example 54

(2-(4-(1,3-Benzodioxolyl-5-methyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-(1-morpholinyl)carbonyl)ethenyl]phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 53B substituting morpholine with 1-piperonylpiperazine. White solid; ^1H NMR (d^6 -DMSO, 300 MHz) δ 2.13-2.40 (br m, 8H), 3.28 (s, 2H), 3.49-3.64 (br m, 6H), 3.54 (s, 2H), 3.70 (br m, 2H), 5.97 (s, 2H), 6.69 (dd, J = 1.8, 8.1 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 15.3 Hz, 1H), 7.33-7.38 (m, 2H), 7.38-7.50 (m, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H). MS (DCI/ NH_3) ($\text{M}+\text{H}$) $^+$ at m/z 592, 594.

Example 55

(2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B substituting morpholine with *N*-isopropyl-1-piperazineacetamide. White solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.04 (d, *J* = 6.3 Hz, 6H), 2.20-2.42 (br m, 8H), 2.78 (s, 2H), 3.47-3.64 (br m, 6H), 3.56 (s, 2H), 3.64-3.76 (br m, 2H), 3.85 (qd, *J* = 6.3, 8.1 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.31-7.39 (m, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.45 (td, *J* = 2.7, 6.3 Hz, 1H), 7.50 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 557, 559.

Example 56

(2-((*N*-Ethoxycarbonylmethyl-*N*-methyl)aminomethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B substituting morpholine with ethyl sarcosinate hydrochloride. White solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 2H), 3.30 (s, 2H), 3.51-3.66 (br m, 6H), 3.66-3.75 (br m, 2H), 3.78 (s, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 15.3 Hz, 1H), 7.33-7.38 (m, 2H), 7.42-7.50 (m, 2H), 7.43 (d, *J* = 15.3 Hz, 1H), 7.53 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 489, 491.

Example 57

(2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

To a stirred solution of the alcohol (368 mg, 0.94 mmol) from Example 11 in 5 mL of anhydrous acetonitrile was added activated 4Å molecular sieves, TPAP (3.3 mg, 0.0094 mmol), and NMO (110 mg, 1.03 mmol). The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then quenched with dimethyl sulfide (100 µL). The crude product was filtered through celite, washed with acetonitrile, condensed in vacuo. The titled compound was purified by silica gel column chromatography to give a white solid (216 mg, 59 %). ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.60 (br m, 6H), 3.73 (br m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 15.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 15.3 Hz, 1H), 7.52 (td, *J* = 1.8, 8.1 Hz, 1H), 7.61 (td, *J* = 1.8, 8.1 Hz, 1H), 7.71 (dd, *J* = 2.1, 8.4 Hz, 1H), 8.02 (dd, *J* = 2.1, 8.4 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 388, 390.

Example 58

(2-(4-Formylpiperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B substituting morpholine with 1-formyl piperazine. White solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.20-2.32 (m, 6H), 2.74 (br m, 2H), 3.48 (s, 2H), 3.59 (m, 6H), 3.70 (br m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.35-7.41 (m, 2H), 7.42 (d, *J* = 15.6

Hz, 1H), 7.45-7.52 (m, 3H), 7.98 (d, $J = 2.1$, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 486, 488.

Example 59

5 (2-(*E*-((1-Morpholinyl)carbonyl)ethenyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

A mixture of bromide (80 mg, 0.18 mmol) from Example 12, acryloylmorpholine (33 mg, 0.23 mmol), Pd(OAc)₂ (2.0 mg, 0.009 mmol), P(*o*-tolyl)₃ (17 mg, 0.056 mmol),
10 Et₃N (39 μ L, 0.27 mmol), and anhydrous DMF (1.0 mL) in a pressure tube was flushed with nitrogen for 5 minutes before it capped and heated at 110 °C over night. TLC indicated almost complete consumption of the starting bromide. The reaction mixture was then allowed to cool down to room temperature, partitioned between EtOAc and water. The aqueous layer was extracted once with EtOAc. The combined organic layer was
15 washed with water and brine, dried over Na₂SO₄, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown solid (35 mg, 39%). ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.43-3.88 (m, 16H), 6.58 (d, $J = 8.7$ Hz, 1H), 7.30 (d, $J = 15.3$ Hz, 2H), 7.43 (d, $J = 15.3$ Hz, 1H), 7.47-7.64 (m, 4H), 7.86 (d, $J = 15.3$ Hz, 1H), 8.06 (d, $J = 2.1$ Hz,
20 1H), 8.14 (d, $J = 7.5$ Hz, 1H). MS (DCI/NH₃) (M+NH₄)⁺ at m/z 516, 518. Analysis calculated for C₂₆H₂₇N₂O₄Cl₁S₁ · 0.46H₂O: C, 61.56; H, 5.55; N, 5.21. Found: C, 61.56; H, 5.50; N, 5.43.

Example 60

(2-Formylphenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 57

- 5 substituting compound from Example 11 with compound from Example 48. Yellow solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.80 (td, *J* = 2.4, 7.5 Hz, 1H), 7.92 (dd, *J* = 2.1, 9.0 Hz, 1H), 8.04 (dd, *J* = 2.4, 7.5 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H), 10.29 (s, 1H). MS (APCI) (M+Cl)⁻ at *m/z* 474, 476.
- 10

Example 61

(2-Formylphenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl]phenyl] sulfide,

N,N-dimethyl hydrazone

- 15 A mixture of the aldehyde (20 mg, 0.052 mmol) from Example 57, 1,1-dimethyl hydrazine (3.9 μL, 0.052 mmol) in 0.5 mL of EtOH with a tiny amount of AcOH was stirred at room temperature over night. The solvent was then removed and the product was purified by preparative TLC to give the titled compound (20 mg, 90%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 2.91 (s, 6H), 3.55-3.82 (br m, 8H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.76 (d, *J* = 15.3 Hz, 1H), 7.05 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.26 (td, *J* = 1.8, 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.47-7.57 (m, 2H), 7.54 (m, 2H), 8.04 (dd, *J* = 1.8, 8.7 Hz, 1H). MS (DCI/NH₃) (M+H)⁺ at *m/z* 430, 432, 434, 436.
- 20

Example 62

(2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

5 A mixture of bromide (60 mg, 0.14 mmol) from Example 12, aminopropylmorpholine (24 μ L, 0.17 mmol), Pd₂(dba)₃ (1.2 mg, 0.0013 mmol), BINAP (2.5 mg, 0.004 mmol), NaOt-Bu (19 mg, 0.20 mmol), 18-crown-6 (50 mg, 0.20 mmol), and anhydrous toluene (1 mL) in a pressure tube was flushed with nitrogen for 3 minutes before it was capped and heated at 80 °C over night. The reaction was then stopped, and
10 allowed to cool down to room temperature. The reaction mixture was partitioned between EtOAc and water, and the aqueous layer was extracted once with EtOAc. The combined organic layer was then washed with water and brine, dried over Na₂SO₄, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown oil (30 mg, 44%).
15 ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.62 (quintet, *J* = 6.5 Hz, 2H), 2.15-2.26 (m, 8H), 3.17 (q, *J* = 6.5 Hz, 2H), 3.22-3.76 (m, 12 H), 3.50 (t, *J* = 6.5 Hz, 2H), 5.72 (t, *J* = 5.7 Hz, 1H), 6.47 (d, *J* = 8.7 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 15.6 Hz, 1H), 7.35-7.42 (m, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H). MS (APCI) (M+H)⁺ at *m/z* 502, 504.

20

Example 63

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)

ethenyl)phenyl] sulfide

Example 63A

(2,4-Dichlorophenyl)[2-amino-4-(E-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)

5 ethenyl)phenyl] sulfide

A mixture of nitro compound (780 mg, 1.58 mmol) from Example 33, SnCl₂ (1.50 g, 7.91 mmol) in 25 mL of anhydrous EtOH was refluxed under nitrogen atmosphere for 90 minutes. The reaction was then allowed to cool down to room temperature, quenched with sat. NaHCO₃, extracted with EtOAc (2x50 mL). The
10 combined organic layer was washed with water and brine, dried over Na₂SO₄, condensed in vacuo to give the crude aniline as yellowish brown solid, which was converted to the bromide without purification.

Example 63B

15 (2,4-Dichlorophenyl)[2-bromo-4-(E-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)

ethenyl)phenyl] sulfide

To a stirred solution of *t*-butyl nitrite (57 µL, 0.48 mmol), CuBr₂ (87 mg, 0.39 mmol) in 2.0 mL of CH₃CN at room temperature was added a solution of aniline from Example 63A (150 mg, 0.323 mmol) in 1.0 mL of CH₃CN. The dark green solution was
20 then heated at 65 °C under nitrogen atmosphere for 90 minutes. The reaction mixture was then allowed to cool down to room temperature, partitioned between EtOAc and 3N HCl. The organic layer was then washed with brine, dried over Na₂SO₄, condensed in

vacuo. The crude product was then purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown solid (50 mg, 29%).

Colorless oil; ¹H NMR (d⁶-DMSO, 300 MHz) δ 1.63 (quintet, *J* = 7.2 Hz, 2H), 1.91 (quintet, *J* = 8.4 Hz, 2H), 2.22 (t, *J* = 8.4 Hz, 2H), 3.09-3.47 (m, 6H), 6.67 (d, *J* = 15.3 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 15.3 Hz, 1H), 7.50 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.57 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 8.13 (t, *J* = 6.0 Hz, 1H). MS (ESI) (M+H)⁺ at *m/z* 527, 529, 531, 533.

Example 64

(2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

Example 64A

[1-Fluoro-2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl) benzene

The title compound was prepared by the procedures described in Example 59 substituting the bromide from Example 12 with 2-fluoro-5-bromobenzaldehyde.

Example 64B

(2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 4-chloro-3-nitro-cinnamide with the compound from Example 64A. White solid; ¹H NMR (d⁶-DMSO, 300 MHz) δ 3.60 (br m, 6H), 3.71 (br m, 2H), 6.82 (d, *J* = 8.7

Hz, 1H), 7.35 (d, J = 15.6 Hz, 1H), 7.54 (d, J = 15.6 Hz, 1H), 7.55 (dd, J = 2.4, 8.7 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 2.4, 8.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H), 10.19 (s, 1H). MS (DCI/NH₃) (M+H)⁺ at m/z 422, 424, 426, 428.

5 Example 65

(2-Chloro-6-formylphenyl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl
ethenyl) phenyl] sulfide

10
11
12
13
14
15
16
17
18
19
20

Example 65A

(2-Carbomethoxyethyl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl
ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with methyl 3-mercaptopropionate, and 6-amino-1-hexanol with 1-acetyl piperazine.

15 Example 65B

(2-Chloro-6-formylphenyl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl
ethenyl) phenyl] sulfide

To a stirred solution of the compound (105 mg, 0.26 mmol) from Example 65A in 2 mL of THF under nitrogen atmosphere at 0 °C was added *t*-BuOK solution (1.0M, 281 μL, 0.29 mmol). Light orange precipitates appeared immediately. After completion of the addition, the reaction mixture was stirred at room temperature for 1 hour before the solvent was removed on a rotavap under reduced pressure.

The yellow thiolate thus obtained was dissolved in 0.5 mL of DMF, and 2,3-dichlorobenzaldehyde was then added. The mixture was then heated at 80 °C under nitrogen for 2 hours. Reaction was then stopped and the solvent was removed under vacuum. The crude product was purified with Gilson Preparative HPLC as described in

- 5 Example 38B to give the titled compound as a white solid (25 mg, 21%). ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (s, 3H), 3.48-3.58 (m, 2H), 3.58-3.84 (m, 6H), 6.53 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 15.3 Hz, 1H), 7.19 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.51-7.62 (m, 2H), 7.60 (d, *J* = 15.3 Hz, 1H), 7.84 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.99 (dd, *J* = 1.8, 8.4 Hz, 1H). MS (APCI) (M+NH₄)⁺ at *m/z* 480, 482, 484.

10

Compounds that antagonize the interaction between ICAM-1 and LFA-1 can be identified, and their activities quantitated, using both biochemical and cell-based adhesion assays. A primary biochemical assay measures the ability of the compound in question to block the interaction between the integrin LFA-1 and its adhesion partner

- 15 ICAM-1, as described below:

ICAM-1 / LFA-1 Biochemical Interaction Assay

- In the biochemical assay, 100 μL of anti-LFA-1 antibody (ICOS Corporation) at a concentration of 5 μg/ml in Dulbecco's phosphate-buffered saline (D-PBS) is used to
20 coat wells of a 96-well microtiter plate overnight at 4°C. The wells are then washed twice with wash buffer (D-PBS w/o Ca⁺⁺ or Mg⁺⁺, 0.05% Tween 20) and blocked by addition of 200 μL of D-PBS, 5% fish skin gelatin. Recombinant LFA-1 (100 μL of 0.7

5 μg/ml, ICOS Corporation) in D-PBS is then added to each well. Incubation continues for
 1 hour at room temperature and the wells are washed twice with wash buffer. Serial
 dilutions of compounds being assayed as ICAM-1/LFA-1 antagonists, prepared as 10
 mM stock solutions in dimethyl sulfoxide (DMSO), are diluted in D-PBS, 2mM MgCl₂,
 10 1% fish skin gelatin and 50 μL of each dilution added to duplicate wells. This is followed
 by addition of 50 μL of 0.8 μg/ml biotinylated recombinant ICAM-1/Ig (ICOS
 Corporation) to the wells and the plates are incubated at room temperature for 1 hour. The
 wells are then washed twice with wash buffer and 100 μL of Europium-labeled
 Streptavidin (Wallac Oy) diluted 1:100 in Delfia assay buffer (Wallac Oy) are added to
 15 the wells. Incubation proceeds for 1 hour at room temperature. The wells are washed
 eight times with wash buffer and 100 μL of enhancement solution (Wallac Oy, cat. No.
 1244-105) are added to each well. Incubation proceeds for 5 minutes with constant
 mixing. Time-resolved fluorimetry measurements are made using the Victor 1420
 Multilabel Counter (Wallac Oy) and the percent inhibition of each candidate compound is
 20 calculated using the following equation:

$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound minus background}}{\text{average OD w/o compound minus background}} \right\}$$

where "background" refers to wells that are not coated with anti-LFA-1 antibody.

20

Compounds of the present invention exhibit inhibitory activity in the above
 assay as follows:

Compound of Example	% inhibition @ 4 μ M
1	75
2	73
3	75
4	72
5	73
6	85
7	87
8	74
9	93
10	79
11	87
12	90
13	79
14	82
15	88
16	86
17	84
18	86

19	93
20	82
21	80
22	90
23	90
24	80
25	82
26	94
27	94
28	87
29	84
30	93
31	92
32	92
33	91
34	91
35	89
36	90
37	91
38	91

39	86
40	90
41	83
42	56
43	82
44	78
45	88
46	87
47	82
48	89
49	93
50	94
51	84
52	86
53	87
54	86
55	82
56	83
57	90
58	80

59	92
60	95
61	88
62	92
63	82
64	81
65	86

Biologically relevant activity of the compounds in this invention is confirmed using a cell-based adhesion assay, which measures their ability to block the adherence of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-1, as follows:

ICAM-1 / JY-8 cell adhesion assay

For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 70 μ L of recombinant ICAM-1/Ig (ICOS Corporation) at a concentration of 5 μ g/mL in D-PBS w/o Ca^{++} or Mg^{++} overnight at 4°C. The wells are then washed twice with D-PBS and blocked by addition of 200 μ L of D-PBS, 5% fish skin gelatin by incubation for 1 hour at room temperature. Fluorescent tagged JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 50 μ L at 2×10^6 cells/ml in RPMI 1640/1% fetal bovine serum) are added to the wells. For fluorescent labeling of JY-8 cells, 5×10^6 cells washed once in RPMI 1640 are

resuspended in 1 mL of RPMI 1640 containing 2 μ M Calcein AM (MolecularProbes), are incubated at 37°C for 30 minutes and washed once with RPMI-1640/ 1% fetal bovine serum. Dilutions of compounds to be assayed for ICAM-1/LFA-1 antagonistic activity are prepared in RPMI-1640/ 1% fetal bovine serum from 10mM stock solutions in DMSO and 50 μ L are added to duplicate wells. Microtiter plates are incubated for 45 minutes at room temperature and the wells are washed gently once with RPMI-1640/ 1% fetal bovine serum. Fluorescent intensity is measured in a fluorescent plate reader with an excitation wavelength at 485 nM and an emission wavelength at 530 nM. The percent inhibition of a candidate compound at a given concentration is calculated using the following equation:

$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

and these concentration/inhibition data are used to generate dose response curves, from which IC₅₀ values are derived. Compounds of the present invention exhibit blocking activity in the above assay as follows:

Compound of Example	IC ₅₀ , nM
1	2,100
2	13,000
3	2,500

ISO 14001:2004

4	680
5	2,900
6	660
7	1,200
8	2,900
9	130
10	1,500
11	260
12	360
13	1,100
14	790
15	140
16	300
17	5,800
18	130
19	450
20	3,300
21	520
22	200
23	600
24	8,000
25	11,000
26	110
27	160
28	370
29	160
30	250
32	190
32	45
33	300
34	70
35	430

36	320
37	140
38	250
39	250
40	280
41	110
42	520
43	100
44	70
45	50
46	60
47	370
48	200
49	20
50	10
51	690
52	420
53	700
54	360
55	100
56	510
57	220
58	1,600
59	200
60	30
61	540
62	340
63	850
65	1,200

Compounds of the present invention have been demonstrated to act via interaction with the integrin LFA-1, specifically by binding to the interaction domain (I-domain), which is known to be critical for the adhesion of LFA-1 to a variety of cell adhesion molecules. As such, it is expected that these compounds should block the interaction of LFA-1 with other CAM's. This has in fact been demonstrated for the case of ICAM-3. Compounds of the present invention may be evaluated for their ability to block the adhesion of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-3, as follows:

10 ICAM-3 / JY-8 cell adhesion assay

For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 50 μ L of recombinant ICAM-3/Ig (ICOS Corporation) at a concentration of 10 μ g/mL in D-PBS w/o Ca^{++} or Mg^{++} overnight at 4°C. The wells are then washed twice with D-PBS, blocked by addition of 100 μ L of D-PBS, 1% bovine serum albumin (BSA) by incubation for 1 hour at room temperature, and washed once with RPMI-1640 / 5% heat-inactivated fetal bovine serum (adhesion buffer). Dilutions of compounds to be assayed for ICAM-3/LFA-1 antagonistic activity are prepared in adhesion buffer from 10 mM stock solutions in DMSO and 100 μ L are added to duplicate wells. JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 100 μ L at 0.75×10^6 cells/ml in adhesion buffer) are then added to the wells. Microtiter plates are incubated for 30 minutes at room temperature; the adherent cells are then fixed with 50 μ L of 14% glutaraldehyde/D-PBS and incubated

5 ELISA plate reader. The percent inhibition of a candidate compound is calculated using the following equation:

$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

- 10 Compounds of the present invention exhibit blocking activity in the above assay as follows:

Compound Of Example	% inhibition @ 0.6 μ M
9	100
12	100
15	100
16	100
17	100
18	100
26	100
27	100
30	100
32	100
34	100
35	100
41	100

45	100
46	100
49	100
50	100
54	100
59	100
60	100
62	100

The ability of the compounds of this invention to treat arthritis can be demonstrated in a murine collagen-induced arthritis model according to the method of Kakimoto, et al., *Cell Immunol* 142: 326-337, 1992, in a rat collagen-induced arthritis model according to the method of Knoerzer, et al., *Toxicol Pathol* 25:13-19, 1997, in a rat adjuvant arthritis model according to the method of Halloran, et al., *Arthritis Rheum* 39: 810-819, 1996, in a rat streptococcal cell wall-induced arthritis model according to the method of Schimmer, et al., *J Immunol* 160: 1466-1477, 1998, or in a SCID-mouse human rheumatoid arthritis model according to the method of Oppenheimer-Marks et al., *J Clin Invest* 101: 1261-1272, 1998.

The ability of the compounds of this invention to treat Lyme arthritis can be demonstrated according to the method of Gross et al., *Science* 281, 703-706, 1998.

The ability of compounds of this invention to treat asthma can be demonstrated in a murine allergic asthma model according to the method of Wegner et al., *Science*

247:456-459, 1990, or in a murine non-allergic asthma model according to the method of Bloemen et al., *Am J Respir Crit Care Med* 153:521-529, 1996.

The ability of compounds of this invention to treat inflammatory lung injury can be demonstrated in a murine oxygen-induced lung injury model according to the method of Wegner et al., *Lung* 170:267-279, 1992, in a murine immune complex-induced lung injury model according to the method of Mulligan et al., *J Immunol* 154:1350-1363, 1995, or in a murine acid-induced lung injury model according to the method of Nagase, et al., *Am J Respir Crit Care Med* 154:504-510, 1996.

The ability of compounds of this invention to treat inflammatory bowel disease can be demonstrated in a rabbit chemical-induced colitis model according to the method of Bennet et al., *J Pharmacol Exp Ther* 280:988-1000, 1997.

The ability of compounds of this invention to treat autoimmune diabetes can be demonstrated in an NOD mouse model according to the method of Hasagawa et al., *Int Immunol* 6:831-838, 1994, or in a murine streptozotocin-induced diabetes model according to the method of Herrold et al., *Cell Immunol* 157:489-500, 1994.

The ability of compounds of this invention to treat inflammatory liver injury can be demonstrated in a murine liver injury model according to the method of Tanaka et al., *J Immunol* 151:5088-5095, 1993.

The ability of compounds of this invention to treat inflammatory glomerular injury can be demonstrated in a rat nephrotoxic serum nephritis model according to the method of Kawasaki, et al., *J Immunol* 150:1074-1083, 1993.

- 5 The ability of compounds of this invention to treat radiation-induced enteritis can be demonstrated in a rat abdominal irradiation model according to the method of Panes et al., *Gastroenterology* 108:1761-1769, 1995.

- 10 The ability of compounds of this invention to treat radiation pneumonitis can be demonstrated in a murine pulmonary irradiation model according to the method of Hallahan et al., *Proc Natl Acad Sci U S A* 94:6432-6437, 1997.

- 15 The ability of compounds of this invention to treat reperfusion injury can be demonstrated in the isolated rat heart according to the method of Tamiya et al., *Immunopharmacology* 29(1): 53-63, 1995, or in the anesthetized dog according to the model of Hartman et al., *Cardiovasc Res* 30(1): 47-54, 1995.

- 20 The ability of compounds of this invention to treat pulmonary reperfusion injury can be demonstrated in a rat lung allograft reperfusion injury model according to the method of DeMeester et al., *Transplantation* 62(10): 1477-1485, 1996, or in a rabbit pulmonary edema model according to the method of Horgan et al., *Am J Physiol* 261(5): H1578-H1584, 1991.

The ability of compounds of this invention to treat stroke can be demonstrated in a rabbit cerebral embolism stroke model according to the method of Bowes et al., *Exp Neurol* 119(2): 215-219, 1993, in a rat middle cerebral artery ischemia-reperfusion model according to the method of Chopp et al., *Stroke* 25(4): 869-875, 1994, or in a rabbit reversible spinal cord ischemia model according to the method of Clark et al., *Neurosurg* 75(4): 623-627, 1991.

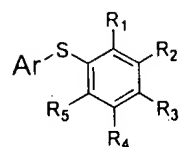
The ability of compounds of this invention to treat peripheral artery occlusion can be demonstrated in a rat skeletal muscle ischemia / reperfusion model according to the method of Gute et al., *Mol Cell Biochem* 179: 169-187, 1998.

The ability of compounds of this invention to treat graft rejection can be demonstrated in a murine cardiac allograft rejection model according to the method of Isobe et al., *Science* 255: 1125-1127, 1992, in a murine thyroid gland kidney capsule model according to the method of Talento et al., *Transplantation* 55: 418-422, 1993, in a cynomolgus monkey renal allograft model according to the method of Cosimi et al., *J Immunol* 144: 4604-4612, 1990, in a rat nerve allograft model according to the method of Nakao et al., *Muscle Nerve* 18: 93-102, 1995, in a murine skin allograft model according to the method of Gorczynski and Wojcik, *J Immunol* 152: 2011-2019, 1994, in a murine corneal allograft model according to the method of He et al., *Ophthalmol Vis Sci* 35: 3218-3225, 1994, or in a xenogeneic pancreatic islet cell transplantation model according to the method of Zeng et al., *Transplantation* 58:681-689, 1994.

CLAIMS

What is claimed is:

- 5 1. A compound of the formula



or a pharmaceutically-acceptable salt or prodrug thereof,

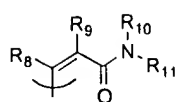
wherein R₁, R₂, R₃, R₄, and R₅ are independently selected from

10

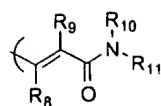
- a. hydrogen,
- b. halogen,
- c. alkyl,
- d. haloalkyl,
- 15 e. alkoxy,
- f. cyano,
- g. nitro,
- h. carboxaldehyde, and

20

with the proviso that at least one of R₁ or R₃ is a "*cis*-cinnamide" or a "*trans*-cinnamide", defined as



"cis-cinnamide"



"trans-cinnamide",

5 wherein R_8 and R_9 are independently selected from

- a. hydrogen, and
- b. alkyl,
- c. carboxy alkyl,
- 10 d. alkylaminocarbonyl alkyl, and
- e. dialkylaminocarbonyl alkyl,

R_{10} and R_{11} are independently selected from

- 15 a. hydrogen,
- b. alkyl,
- c. cycloalkyl,
- d. alkoxy carbonyl alkyl,
- c. hydroxyalkyl, and
- 20 f. heterocyclalkyl,

or where $NR_{10}R_{11}$ is heterocyclyl or substituted heterocyclyl, where
substituents are independently selected from

- 1) alkyl,
- 2) alkoxy,
- 3) alkoxyalkyl,
- 4) cycloalkyl,
- 5) aryl,
- 6) heterocyclyl,
- 7) heterocyclylcarbonyl,
- 8) heterocyclylalkylaminocarbonyl,
- 9) hydroxy,
- 10) hydroxyalkyl,
- 11) hydroxyalkoxyalkyl,
- 12) carboxy,
- 13) carboxycarbonyl,
- 14) carboxaldehyde,
- 15) alkoxycarbonyl,
- 16) arylalkoxycarbonyl,
- 17) aminoalkanoyl,
- 18) carboxamido,
- 19) alkoxycarbonylalkyl,
- 20) carboxamidoalkyl,

- 21) alkanoyl,
- 22) hydroxyalkanoyl,
- 23) alkanoyloxy,
- 24) alkanoylamino,
- 25) alkanoyloxyalkyl, and
- 26) alkylsulfonyl,

and wherein **Ar** is a substituted aryl or substituted heteroaryl group, where substitutions are independently selected from

- a. hydrogen,
- b. halogen,
- c. alkyl,
- d. aryl,
- e. haloalkyl,
- f. hydroxy,
- g. alkoxy,
- h. alkoxycarbonyl,
- i. alkoxyalkoxy,
- j. hydroxyalkyl,
- k. aminoalkyl,
- l. alkyl(alkoxycarbonylalkyl)aminoalkyl,

- m. heterocyclalkyl,
- n. substituted heterocyclalkyl,,
- o. carboxaldehyde,
- p. carboxaldehyde hydrazone,
- 5 q. carboxamide,
- r. alkoxycarbonyl alkyl,
- s. hydroxycarbonylalkyl (carboxyalkyl),
- t. cyano,
- u. amino,
- 10 v. heterocyclalkylamino, and
- w. "*trans*-cinnamide",

or a pharmaceutically-acceptable salt or prodrug thereof.

- 15 2. A compound according to Claim 1 wherein R₁ is a "*cis*-cinnamide" or a "*trans*-cinnamide", and R₃ is hydrogen.
- 3. A compound according to Claim 1 wherein R₃ is a "*cis*-cinnamide" or a "*trans*-cinnamide", and R₁ is hydrogen.
- 20 4. A compound according to Claim 1 wherein R₃ is a "*cis*-cinnamide" or a "*trans*-cinnamide", and R₁, R₈, and R₉ are hydrogen.

5. A compound according to Claim 4 wherein R₃ is a "*cis*-cinnamide".
6. A compound according to Claim 4 wherein R₃ is a "*trans*-cinnamide".
7. A compound according to Claim 1 wherein R₃ is a "*cis*-cinnamide" or a "*trans*-cinnamide", R₁, R₂, and R₄ are each independently hydrogen or alkyl; and R₃ is selected from halogen, haloalkyl, and nitro.
8. A compound according to Claim 4 wherein Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl.
9. A compound according to Claim 4 wherein R₁₀ and R₁₁ are each independently selected from hydrogen, alkyl, cycloalkyl, alkoxycarbonylalkyl, hydroxyalkyl, and heterocyclalkyl.
10. A compound according to Claim 4 wherein NR₁₀R₁₁ is heterocyclyl or substituted heterocyclyl.
11. A compound according to Claim 8 wherein Ar is selected from substituted phenyl, 1,3-benzimidazol-2-one, 1,4-benzodioxane, 1,3-benzodioxole, 1-benzopyr-2-en-4-one, indole, isatin, 1,3-quinazolin-4-one, and quinoline..

5
10
15
20

12. A compound according to Claim 11 wherein R_3 is a "trans-cinnamide"; and **Ar** is selected from 1,3-benzimidazol-2-one, 1,4-benzodioxane, 1,3-benzodioxole, 1-benzopyr-2-en-4-one, indole, isatin, phenyl, 1,3-quinazolin-4-one, and quinoline.

13. A compound according to Claim 12 wherein R_{10} and R_{11} are independently selected from hydrogen, alkyl, cycloalkyl, alkoxyalkyl, hydroxyalkyl, and heterocyclylalkyl.

14. A compound according to Claim 12 wherein $NR_{10}R_{11}$ is heterocyclyl or substituted heterocyclyl as described above.

15. A composition comprising a compound of claim 1 in a pharmaceutically-acceptable carrier.

16. A method of inhibiting inflammation comprising the administration of a compound of claim 1 to a patient.

17. A method of inhibiting inflammation comprising the administration of a composition of claim 15 to a patient.

18. A method of suppressing immune response comprising the administration of a compound of claim 1 to a patient.

19. A method of suppressing immune response comprising the administration of a composition of claim 15 to a patient.

6014097-122998

Abstract

The present invention relates to novel cinnamide compounds that are useful for treating inflammatory and immune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune

5 response in a mammal.

60114097 1229000



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
60/114,097	12/29/1998		150	6446.US.Z1			

STEVEN F WEINSTOCK
 ABBOTT LABORATORIES
 DEPT 377 AP6D
 100 ABBOTT PARK ROAD
 ABBOTT PARK, IL 600643500

CONFIRMATION NO. 1913

REPLACEMENT FILING RECEIPT



OC000000011122759

Date Mailed: 10/28/2003

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

JAMES LINK, EVANSTON, IL;
 GANG LIU, GURNEE, IL;
 ZHONGHUA PEI, LIBERTYVILLE, IL;
 TOM VON GELDERN, RICHMOND, IL;
 MARTIN WINN, DEERFIELD, IL;
 ZHILI XIN, GURNEE, IL;

If Required, Foreign Filing License Granted: 01/26/1999

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

CELL ADHESION-INHIBITING ANTIINFLAMMATORY AND IMMUNE-SUPPRESSIVE
 COMPOUNDS

LICENSE FOR FOREIGN FILING UNDER

Titl 35, United States Code, Section 184
Titl 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).